

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Escaping NK cells and recruiting neutrophils: How Morgana/NF-B signaling promotes metastasis

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1730759> since 2021-09-29T09:38:23Z

Published version:

DOI:10.1080/23723556.2018.1432258

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Escaping NK cells and recruiting neutrophils: how Morgana/NF- κ B axis promotes metastasis

Federica Fusella¹, Laura Seclì¹ and Mara Brancaccio¹

¹Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino 10126, Italy.

Correspondence should be addressed to F.F. (federica.fusella@unito.it) or to M.B. (mara.brancaccio@unito.it).

Cancer cells escape immune surveillance and induce immune cell aberrant activation to support tumour growth and progression. We recently reported that Morgana/NF- κ B axis in breast cancer cells is responsible for NK inactivation and neutrophil recruitment in the primary tumour and in the lung pre-metastatic niche.

Keywords: Morgana, breast cancer metastasis, NF- κ B, Natural Killer cells, neutrophils

Metastatic breast cancer is the second leading cause of cancer death in women. Despite the advance in diagnostic methods, the mortality for this cancer remains high. Patient death results entirely from metastasis formation in distant organs. 10-15% of patients have an aggressive tumour and develop metastasis within 3 years (1). Understanding the molecular pathways activated or de-regulated in cancer cells becomes fundamental to study and block cancer progression. Numerous genes are involved in this complex process that includes several steps starting from tumour cell proliferation, migration, vessel invasion, resistance from anoikis, extravasation and finally colonization of distant organs. Morgana is a protein ubiquitarily expressed and essential for embryonic development and involved in tumorigenesis (2). Morgana is frequently overexpressed in aggressive and chemo resistant breast tumours (as triple negative breast tumours) and it positively correlates with tumour grade, proliferative capacity, and lymph node involvement (3,4). Tumour progression and metastasis formation are strongly influenced by bidirectional communication between cancer cells and cells resident in the tumour microenvironment as immune system cells, fibroblasts and endothelial cells (5). In our recent work, we demonstrated how the axis Morgana-NF- κ B can control and mediate the cross-talk between tumour and cell microenvironment (6).

High Morgana expression levels in cancer cells can shape immune cell recruitment both in the tumour and in distant organs site of metastasis. In particular, we show that in the first phases of tumour growth Morgana inhibits Natural Killer (NK) cell recruitment. Several mechanisms can be used by tumour cells to escape immunosurveillance mediated by NK cells, in fact most tumours retained expression of MHC class I or tumours themselves can secrete immunomodulatory molecules specifically compromising NK activity (7). High Morgana levels in breast cancer cells induce MHC class I expression, leading to NK inhibition and immunoevasion (6). Looking at immune system cell recruitment in later phases of tumour progression, a significant reduction of neutrophils was observed in low Morgana tumours. Emerging evidences indicate that chemokine produced by the tumour can polarize neutrophils toward a pro-tumour phenotype, able to promote primary tumour growth and spread (8). The explanation of this differential immune system cell recruitment in the primary tumour resides in the ability of Morgana to control the activation of one of the most studied transcription factor: NF- κ B. NF- κ B represents a central player in inflammation, stress response, cell differentiation and proliferation. It controls the expression of a huge variety of target genes such as cytokines, growth factors, adhesion molecules, intracellular signalling molecules, transcription factors as well as miRNAs (9). Usually NF- κ B is maintained inactive in the cytosol by its inhibitor I κ B (inhibitors of NF- κ B). Upon several specific stimuli, I κ B proteins are phosphorylated by the canonical IKK complex on two specific serines, which then act as a docking platform for the ubiquitin ligase b-TRCP. Subsequent ubiquitination induces proteasome-mediated proteolysis of the I κ B protein and, subsequently, NF- κ B is free and capable of entering the nucleus, binding DNA and activating transcription. The crucial mediator of the canonical pathway able to activate NF- κ B is the IKK complex, composed by the kinase subunits IKK α and IKK β and the regulatory subunit IKK γ (9). In our work we described for the first time Morgana as a component of the IKK complex necessary to mediate the binding between the IKK complex and its substrate I κ B α both in tumorigenic (human MDA-MB-231, BT549, Hela, MCF10A, MCF7, and murine 4T1 and E0771) and normal cell lines (293T, NIH and primary mouse embryonic fibroblasts) (6). In breast cancer models, Morgana, by potentiating NF- κ B activation and the subsequent transcription of its target genes, favours cancer cell invasion and metastasis formation (Figure 1). In fact, Morgana downregulation almost completely abrogates MDA-MB-231, 4T1 and E0771 abilities to form metastasis. Immune system cells have an important role not only in promoting tumour growth and spread, but also in metastasis formation.

Several reports demonstrated that neutrophils can localize in the lung pre-metastatic niche creating a favourable environment to drive metastasis initiation (10). Morgana downregulation in breast cancer cells, by quenching NF- κ B signalling, inhibits neutrophil recruitment and the formation of the pre-metastatic niche in the lung. Furthermore, NF- κ B activation, through I κ B α silencing, in cancer cells downregulated for Morgana totally rescues primary tumour growth, neutrophil recruitment and metastasis formation, demonstrating a causal role of Morgana/NF- κ B axis in these events. Bioinformatics studies on TCGA breast cancer dataset, coupled with analysis on our cohort of 152 breast cancer patients, confirmed a correlation between Morgana expression levels, NF- κ B activation, neutrophils recruitment and poor survival in human breast cancer patients (6). NF- κ B is frequently overexpressed in cancer and tumour infiltrating immune cells produce cytokines that further sustain NF- κ B activation in cancer cells, generating a vicious cycle difficult to break down. Several NF- κ B inhibitors have been produced but the major concern in using these molecules in cancer therapy rely in robust immunosuppression due to NF- κ B pleiotropic functions in immune responses. In this view, dissecting the precise network of signals originating from NF- κ B pathway and the factors responsible for its activation in cancer cells could open new horizons to develop druggable targets able to shut down the vicious cycle and to block cancer progression.

Funding:

This work was supported by AIRC 2014 (IG 15880) to M.B. and F.F. was supported by a fellowship from FIRC (triennial fellowship “Cecilia Tocco”).

Conflict of interest:

The authors report no conflict of interest.

Figure 1: Morgana/NF- κ B axis in breast cancer cells induces tumour growth and metastasis formation

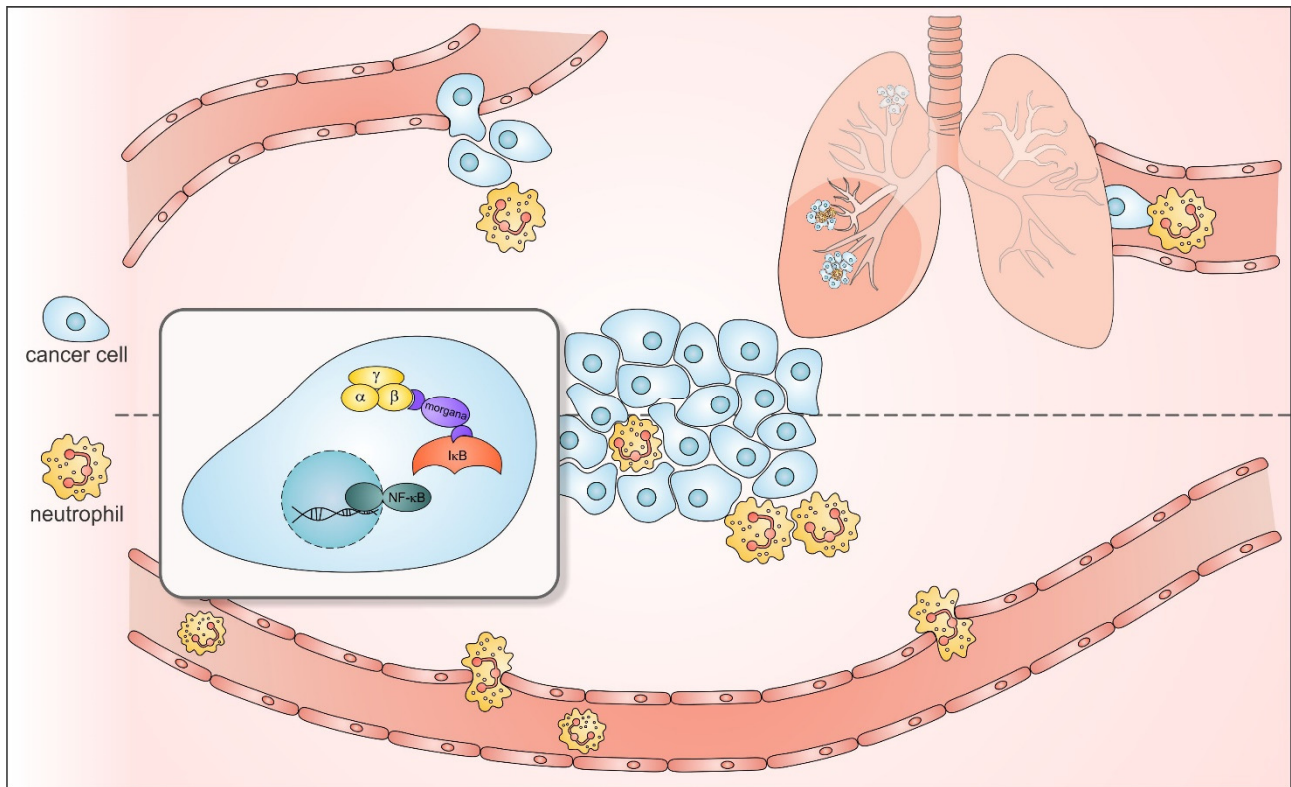


Figure 1. Morgana is necessary to connect the IKK complex to its substrate I κ B α . The consequent activation of NF- κ B in the primary tumour induces the production of several cytokines able to modulate the recruitment of immune cells promoting metastasis progression.

References:

1. Weigelt B, Peterse JL, Van't Veer LJ. Breast cancer metastasis: Markers and models. *Nat Rev Cancer*. 2005;5(8):591–602.
2. Ferretti R, Sbroggiò M, Di Savino A, Fusella F, Bertero A, Michowski W, et al. Morgana and Melusin: Two fairies chaperoning signal transduction. *Cell Cycle*. 2011;10(21):3678–83.
3. Fusella F, Ferretti R, Recupero D, Rocca S, Di Savino A, Tornillo G, et al. Morgana acts as a proto-oncogene through inhibition of a ROCK-PTEN pathway. *J Pathol*. 2014;234(2):152–63.
4. Brancaccio M, Rocca S, Seclì L, Busso E, Fusella F. The double face of Morgana in tumorigenesis. *Oncotarget* [Internet]. 2015;6(40):42603–12. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26460959>
5. Quail D, Joyce J. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* [Internet]. 2013;19(11):1423–37. Available from: <http://www.nature.com/nm/journal/v19/n11/abs/nm.3394.html>
6. Fusella F, Seclì L, Busso E, Krepelova A, Moiso E, Rocca S, et al. The IKK/NF- κ B signaling pathway requires Morgana to drive breast cancer metastasis. *Nat Commun* [Internet]. 2017;8(1):1636. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29158506> <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5696377>
7. Morvan MG, Lanier LL. NK cells and cancer: You can teach innate cells new tricks. *Nat Rev Cancer* [Internet]. 2016;16(1):7–19. Available from: <http://dx.doi.org/10.1038/nrc.2015.5>
8. Coffelt SB, Wellenstein MD, De Visser KE. Neutrophils in cancer: Neutral no more. *Nat Rev Cancer* [Internet]. 2016;16(7):431–46. Available from: <http://dx.doi.org/10.1038/nrc.2016.52>
9. Hoesel B, Schmid JA. The complexity of NF- κ B signaling in inflammation and cancer. *Mol Cancer* [Internet]. 2013;12(1):86. Available from: <http://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-12-86>
10. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: Organ-specific homes for metastases. *Nat Rev Cancer* [Internet]. 2017;17(5):302–17. Available from: <http://dx.doi.org/10.1038/nrc.2017.6>